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Abstract: BACKGROUND Since 2010, combination therapy with gemcitabine and cisplatin is the standard treatment for patients with biliary tract cancer (BTC) based on the ABC-02 trial. However, treatment after first-line progression is less clearly defined. We therefore retrospectively analyzed the efficacy of a 3-drug chemotherapy regimen in patients with advanced BTC. METHODS Patients with advanced BTC treated with palliative chemotherapy between April 2000 and October 2005 at Regensburg University Hospital were reviewed retrospectively. We analyzed the efficacy and safety of an institutional standard 3-drug regimen consisting of irinotecan, gemcitabine and 5-FU (IGF). One cycle, lasting 21 days, included applications on days 1 and 8 consisting of 75 mg/m² irinotecan i.v. for 90 min, 1,000 mg/m² gemcitabine i.v. for 30 min and 2,000 mg/m² fluorouracil (5-FU) for 24 h. RESULTS A total of 12 histologically confirmed cases with gallbladder cancer and intrahepatic BTC were reviewed. Fifty percent of the patients (6/12) had been pretreated with other chemotherapies. Median progression-free survival was 9.4 months (1.5-21.5) and median overall survival was 17.2 months (2.5-24.3). Only neutropenia (8%) was observed as an NCI-CTC grade 3 toxicity. Anemia and leucopenia grades 1 and 2 were the most common side effects. CONCLUSIONS The combination of IGF shows a promising survival benefit with manageable toxicity in patients with advanced BTC. Therefore, this regimen seems to be a feasible second-line treatment option for patients with rapid progression under first-line therapy with gemcitabine and cisplatin and with a good performance status.

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Irinotecan Plus Gemcitabine and Fluorouracil in Advanced Biliary Tract Cancer: A Retrospective Study

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Key Words

Biliary tract cancer · Chemotherapy · Irinotecan · Gemcitabine · Fluorouracil

Abstract

Background: Since 2010, combination therapy with gemcitabine and cisplatin is the standard treatment for patients with biliary tract cancer (BTC) based on the ABC-02 trial. However, treatment after first-line progression is less clearly defined. We therefore retrospectively analyzed the efficacy of a 3-drug chemotherapy regimen in patients with advanced BTC. **Methods:** Patients with advanced BTC treated with palliative chemotherapy between April 2000 and October 2005 at Regensburg University Hospital were reviewed retrospectively. We analyzed the efficacy and safety of an institutional standard 3-drug regimen consisting of irinotecan, gemcitabine and 5-FU (IGF). One cycle, lasting 21 days, included applications on days 1 and 8 consisting of 75 mg/m² irinotecan i.v. for 90 min, 1,000 mg/m² gemcitabine i.v. for 30 min and 2,000 mg/m² fluorouracil (5-FU) for 24 h. **Results:** A total of 12 histologically confirmed cases with gallbladder cancer and intrahepatic BTC were reviewed. Fifty percent of the patients (6/12) had been pretreated with other chemotherapies. Median progression-free survival

was 9.4 months (1.5–21.5) and median overall survival was 17.2 months (2.5–24.3). Only neutropenia (8%) was observed as an NCI-CTC grade 3 toxicity. Anemia and leucopenia grades 1 and 2 were the most common side effects. **Conclusions:** The combination of IGF shows a promising survival benefit with manageable toxicity in patients with advanced BTC. Therefore, this regimen seems to be a feasible second-line treatment option for patients with rapid progression under first-line therapy with gemcitabine and cisplatin and with a good performance status.

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Introduction

Cholangiocarcinoma are rare tumors with poor prognosis [1]. They originate intrahepatic or extrahepatic from the bile duct epithelium. Hilar carcinomas are known as Klatskin tumors. Gallbladder cancers are also associated with an unfavorable prognosis [2]. Surgery is the only curative treatment option with 5-year survival rates of 0–40% after R0 resection [3–5]. In advanced,

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nonresectable tumors, the median overall survival (OS) for these patients is 3–6 months [1, 6, 7].

Palliative therapy options are limited. Systemic chemotherapy with gemcitabine was the mainstay of treatment in advanced biliary tract cancer (BTC) for a long time. Median survival was about 6 months in different phase II studies [8].

In 2010, the first phase III randomized controlled multicenter trial (ABC-02) demonstrated a significant survival advantage for cisplatin plus gemcitabine compared with gemcitabine alone without an increase in toxicity [9]. In this study, 410 patients with locally advanced or metastatic BTC were randomly assigned to receive either cisplatin plus gemcitabine or gemcitabine alone. The median OS was 11.7 months in the combination group and 8.1 months in the gemcitabine group. Since this time, this combination therapy is the standard of care for the treatment of patients with advanced BTC.

A systematic review on gemcitabine and cisplatin for advanced BTC including one meta-analysis, 4 randomized controlled trials, 12 nonrandomized prospective studies and 3 retrospective studies supported the efficacy and safety of this combination [10]. Median OS ranged from 4.6 to 11.7 months without substantial toxicity.

Recently, a comprehensive analysis of 83 prospective trials in advanced BTC demonstrated that the combination of gemcitabine with platinum agents compared with other regimens shows a strong trend toward improved response rate, but no significant difference in progression-free survival (PFS) or OS [11]. Since the global effect of gemcitabine showed a strong statistical trend in OS and significant improvement in PFS while platinum containing regimens did not, this clinical effect seems mainly to be due to gemcitabine. Furthermore, in this study, gemcitabine-based combination therapies containing 5-FU showed a strong trend toward an improved OS (9.5 vs. 12.5 months) relative to platinum agents. To date, a randomized phase III trial comparing gemcitabine and cisplatin vs. gemcitabine plus 5-FU is lacking.

Treatment protocols after first-line progression are less clearly defined. Depending on the first-line setting, 2-drug combinations of gemcitabine and 5-FU or platinum and 5-FU plus oxaliplatin or irinotecan are commonly used [12–14]. Irinotecan is a DNA topoisomerase I inhibitor, which has synergistic activity with 5-FU and gemcitabine [15]. Therefore, we retrospectively evaluate the efficacy of a palliative 3-drug chemotherapy protocol consisting of irinotecan, gemcitabine and 5-FU (IGF) in patients with nonresectable BTC.

Patients and Methods

Patients

We retrospectively analyzed individual chart reviews of 12 patients with histologically confirmed, nonresectable BTC, who were treated with a palliative chemotherapy consisting of IGF between April 2000 and October 2005 at the university clinic of Regensburg. Written consent was obtained in each case.

IGF regimen consisted of 75 mg/m² irinotecan at a 90-min infusion on days 1 and 8, followed by 1,000 mg/m² gemcitabine at a 30-min infusion on days 1 and 8 and continuous infusion for 24 h of 2,000 mg/m² 5-fluorouracil (days 1 and 8). This cycle was given every 21 days.

Tumor response was evaluated with CT scans usually performed every 2 cycles. Tumor response was evaluated and graded using WHO criteria [16]. A complete response (CR) per site was defined as the complete disappearance of the disease. A partial response (PR) was defined as a >50% decrease in the total lesion size without appearance of new lesions. Progressive disease (PD) was characterized either as a ≥25% increase in lesion size or appearance of new lesions. Stable disease (SD) was defined as a CR, PR or PD not demonstrated ≥3 weeks after starting treatment.

We excluded 2 patients from tumor response analysis: 1 patient received only one cycle of chemotherapy and was not available for response evaluation due to rapid progression. Another patient was not included because of a diagnosis of a second tumor (colorectal cancer) during chemotherapy.

Statistical Analysis

Response rate, PFS, OS and safety were measured. Patients who received at least one infusion were assessable for safety. For hematologic and biologic parameters, at least one measurement per cycle was required. OS was defined as the time from the beginning of chemotherapy until death. PFS was defined as the time from the beginning of chemotherapy until disease progression or death, whichever occurred first. The duration of response was calculated as the time from the beginning of chemotherapy to progression.

The Kaplan–Meier method was used to estimate OS and PFS outcomes. Statistical analysis was performed using the SPSS program (version 12.0 for Windows).

Results

Patient Characteristics

From April 2000 to October 2005, 12 patients were enrolled in the study. The baseline characteristics of the 12 treated patients are listed in table 1. Fifty-eight percent female and 42% male patients were treated. The median age was 69 (range 49–73 years). Seventy-five percent (9/12) of patients had intrahepatic cholangiocarcinoma; 25% (3/12) had gallbladder cancer.

Six of 12 patients (50%) were pretreated with different chemotherapy protocols with pioglitazone, rofecoxib, capecitabine, gemcitabine and oxaliplatin (table 1).

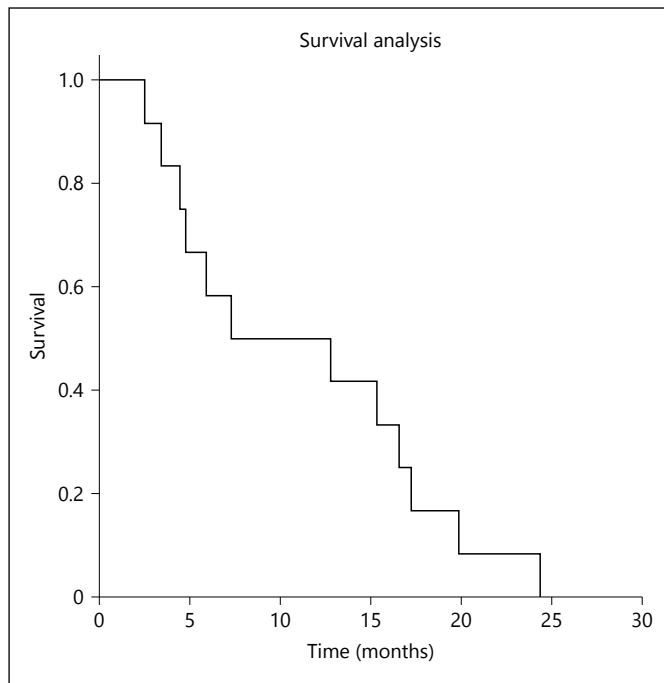


Fig. 1. Kaplan–Meier estimates of OS.

Treatment Administration

A total of 80 cycles were completed (median 5 cycles per patient; range 1–16 cycles). All patients received at least one dose of chemotherapy and were eligible for safety analysis. The median dose-intensity was 99% for irinotecan (50.7–101.8%), 100% for gemcitabine (50.0–100.0%) and 100% for 5-FU (49.5–100.5%).

Toxicity

Twelve patients could be assessed for safety. No treatment-related deaths occurred. NCI-CTC grades 3 and 4 toxicity were rare. Severe hematologic toxicities were observed only with respect to neutropenia (grade 3: 8%). Anemia grades 1 and 2 were regarded as a common side effect of the chemotherapy (8/12, 67% and 3/12, 25%, respectively). Despite antiemetic medication, nausea affected most of the patients. Sixty-seven percent (8/12) of patients suffered from nausea. Grade 1 vomiting was observed in 33% (4/12) of patients and grade 2 in 17% (2/12) of patients. Three patients (25%) experienced diarrhea grades 1 and 2 and only 1 patient (8%) had grade 3.

Objective Response and Survival

Ten patients could be assessed for response analysis (table 2; fig. 1). No objective treatment responses or regression of tumors were observed. Seven patients (70%)

Table 1. Characteristics of treated patients

Number of patients	n = 12	%
Gender		
Male	5	41.7
Female	7	58.3
Age, years		
Median	69	–
Range	49–73	–
Localization of the primary tumor		
Intrahepatic cancer	9	75
Gallbladder cancer	3	25
Prior treatment		
None	5	41.7
Operative resection	1	8.3
Chemotherapy*	6	50

* Different chemotherapy protocols with pioglitazone, rofecoxib, capecitabine, gemcitabine and oxaliplatin.

Table 2. Efficacy results

	Anzahl	%
Tumor response after 6 cycles (n = 10)		
CR	0	0
PR	0	0
SD	7	70
PD	3	30
Time to tumor progression (n = 12), months		
Median	9.436	
Range	1.51–21.53	
OS (n = 12), months		
Median	17.24	
Range	2.50–24.32	

had SD. For survival analysis all 12 patients were included: median PFS was 9.4 months (1.5–21.5); median OS was 17.2 months (2.5–24.3).

Discussion

BTC is a rare and aggressive tumor. The treatment of metastatic BTC still remains a challenge. In our retrospective analysis of patients with advanced BTC, we evaluated the efficacy and safety of a 3-drug regimen consisting of IGF. While the response rate was 0, 70% of patients had SD with a promising median PFS of 9.4 months and a median OS of 17.2 months. There were no grade 4 tox-

ities, and grade 3 side effects such as leucopenia were found only in 1 patient (8%).

There are few published reports about the treatment of advanced BTC with 3-drug combinations and to our knowledge determined only in first-line treatment so far: Petrioli et al. [17] could show that 3-weekly oxaliplatin combined with gemcitabine and oral capecitabine in the first-line treatment of 37 patients with advanced BTC is an active and well-tolerated chemotherapy regimen. The overall response rate was 35% and the disease control rate was 73%. The median PFS was 9.4 months (95% CI 4.1–12.2 months) and the median OS was 13.8 months (95% CI 7.7–17.1 months). Analogous to our study, there were no grade 4 toxicities and grade 3 neutropenia in 13.5% of patients and grade 3 thrombocytopenia in 10.8%.

In a multi-institution phase II study, Kanai et al. [18] evaluated the efficacy and safety of gemcitabine/cisplatin/S-1 combination chemotherapy in 50 patients with advanced BTC. Comparable to our data, the median OS was promising with 16.2 months. Toxicity was manageable with grades 3–4 neutropenia in 32%, anemia in 32% and thrombocytopenia in 10%. Febrile neutropenia occurred in 4%.

In 2010, Yamashita et al. [19] also reported a significant antitumor activity of gemcitabine/5-FU/cisplatin in

21 patients with advanced BTC: median OS was 18.8 months and PFS was 13.4 months. Hematological grade 3 toxicity, such as leucopenia, thrombocytopenia and anemia, was found in 6 patients (28.6%).

A further small study on 14 patients with advanced BTC could demonstrate an overall response rate of 21.4% with a triple combination chemotherapy consisting of gemcitabine, 5-FU and cisplatin [20]. SD was observed in 64.3% and clinical benefit in even 85.7%.

On the other hand, Wagner et al. [21] achieved comparable results for response and survival to previously reported regimens (median OS 10 months) with the combination of gemcitabine, oxaliplatin and 5-FU in patients with advanced BTC and gallbladder cancer, but with more toxicity.

However, according to others (17–20), a 3-drug combination chemotherapy was a safe and feasible treatment option in the second-line setting, which resulted in a clinically relevant stabilization rate in the pretreated patients with advanced BTC. Consequently, IGF might be a helpful treatment option for patients with BTC and a good performance status after rapid progression under first-line therapy with gemcitabine and cisplatin.

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